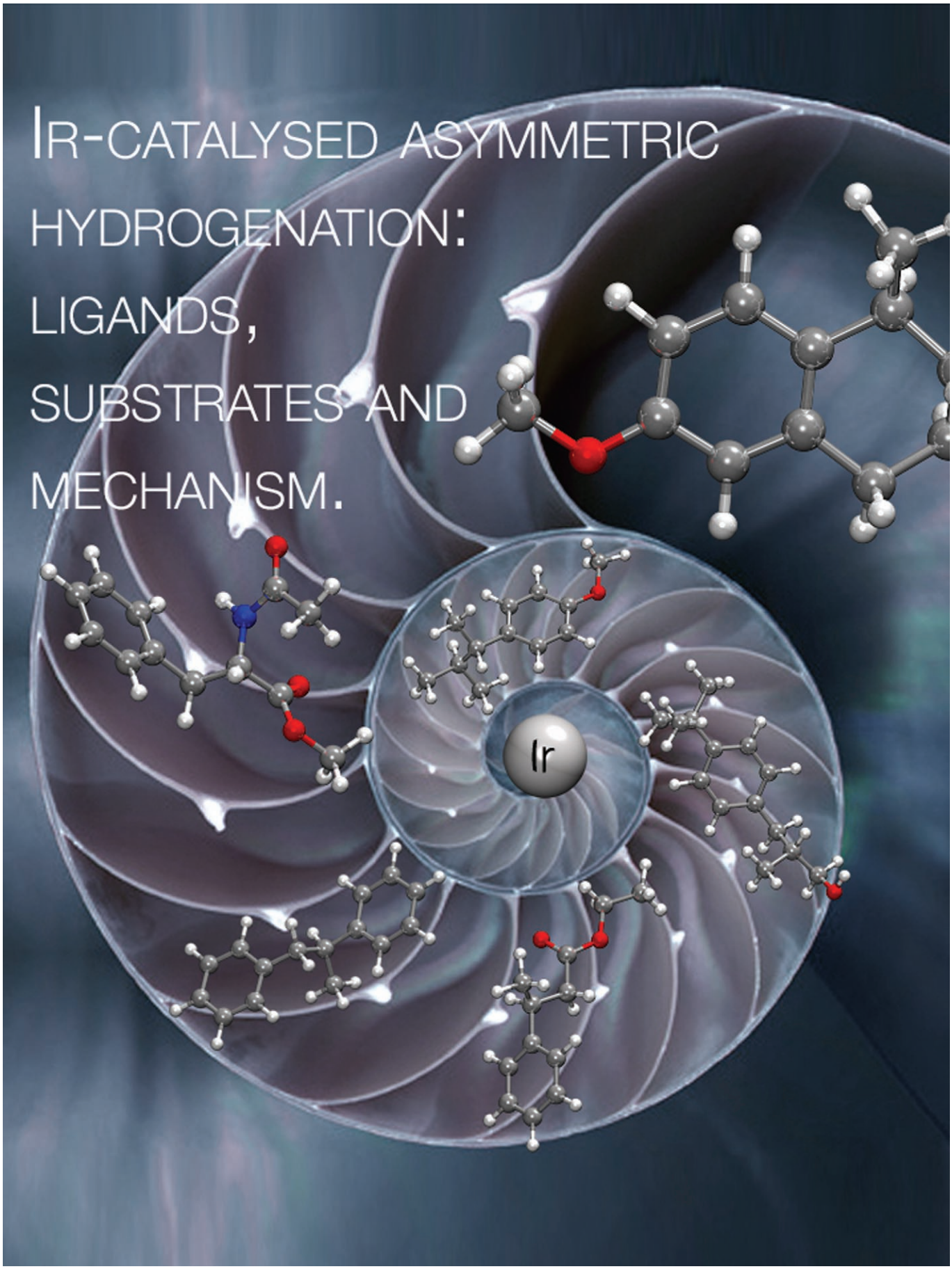

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Ir-Catalysed Asymmetric Hydrogenation: Ligands, Substrates and Mechanism

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Dedicated to Professor David Tanner on the occasion of his 50th birthday

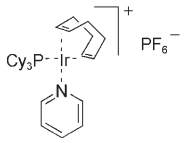
Abstract: Relatively air and moisture tolerant cationic iridium complexes, with chiral non-racemic N,P-ligands and weakly coordinating counter ions, are efficient catalysts in the asymmetric hydrogenation of olefins. Unfunctionalised olefins are particularly difficult substrates because, in general, a polar group adjacent to the alkene bond is required for high catalytic activity and enantioselectivity. The applicability towards a variety of substrates and choice of ligands reported thus far in the literature, as well as the mechanism, selectivity issues and the importance of the anion are also discussed.

Keywords: asymmetric catalysis · density functional calculations · hydrogenation · iridium · olefins

Introduction

Enantioselective hydrogenation is one of the most powerful methods in asymmetric catalysis. While ruthenium- and rhodium-catalysed asymmetric hydrogenations of chelating olefins have a long history,[1] unfunctionalised olefins still represent a challenging class of substrates. During the last few years, Pfaltz and others have developed chiral mimics of Crabtree's catalyst,[2] which have been used successfully for the asymmetric hydrogenation of aryl alkenes.[3] However, asymmetric hydrogenation is still highly substrate dependent and the development of new efficient chiral complexes that tolerate a broad range of substrates remains a challenge.

Crabtree reported the first homogeneous achiral iridium catalysis in 1977 ([**A**], Figure 1) where he was able to reduce a range of unfunctionalised olefins, including tri- and tetrasubstituted with good turnover frequency (TOF).[4] He isolated an active catalytic species of the type $[IrH_2(olefin)_2L_2]^+$, which could collapse directly to the alkane without further associative or disassociative steps.[2] It was also observed that a competing reaction takes place along side the catalytic cycle, the deactivation of the active species. When utilizing a mixed ligand system a catalytically inactive Ir-trimer is formed [Eq. (1), L = PCy_3, L′ = pyridine, COA = cyclooctane].[2]



[A]

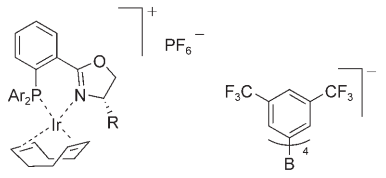
Figure 1. Crabtree's homogeneous mixed ligand Ir-complex [**A**].

$$3\,[Ir(cod)LL']PF_6 + 10\,H_2 \rightarrow [(H_2LL'Ir)_3(\mu_3\text{-}H)]PF_6 + HPF_6 + 3\,COA \quad (1)$$

Never the less his initial work served as a starting point for the search of more potent catalysts.

Ir-Catalysed Hydrogenation of Olefins

With a few exceptions, Rh, Ru and Buchwald's titanocene complexes,[5a,b] it took a further 21 years until Pfaltz and coworkers reported the successful asymmetric Ir-catalysed hydrogenation of unfunctionalised olefins ([**B**], Figure 2) utiliz-



[B] [C]

Figure 2. [**B**] Pfaltz first-generation complex. [**C**] The counterion BAr_F.

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ing a previously reported phosphine–oxazoline ligand.[6] This complex gave encouraging results but was limited in terms of the scope of the substrate and the deactivation of the Ir complex, presumably through a similar formation of inactive hydride-bridged trimers as reported by Crabtree.[2a] Two iridium trinuclear hydride clusters, prepared from [Ir(1,5-cod)(**I**)](OTf), have been recently reported by Smidt et al. and shown to be inactive as hydrogenation catalysts.[2b] Pfaltz reported that through the use of strictly anhydrous and anaerobic conditions full conversion of a substrate could be obtained with catalyst loadings of only 0.5 mol %.[7] However, at this level of catalyst loadings it was still difficult to avoid deactivation. Through the simple exchange of the PF_6^- counterion with the even more weakly coordinating anion tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) [**C**] it was found that the Ir complexes were more robust and allowed catalyst loading as low as 0.02 mol %.[7,28]

Ligands

Since this first report by Pfaltz there have been many reports of variations to the N,P-ligand utilised in [**B**] which have been successfully employed in the hydrogenation of olefins (Table 1, entries 1–8).[8] Phosphine-oxazoline ligand **I**, originally employed by Pfaltz in asymmetric hydrogenation,[7] has evolved into many different classes of successful ligands. Extensive variations of the aromatic group linking the oxazoline and phosphine moieties has proven to be successful, **II**–**IV** (Figure 3).[9b,11,12] Burgess exchanged the phosphine with a carbene **V** (Figure 3)[13] and employed it as a ligand with great success, showing that N,P-based ligands are not essential. However, ligand **I** even after extensive variations still proved to be limited in the scope of the substrate. Pfaltz subsequently developed a new class of ligands **VII**–**IX** (Figure 3), which were found to be tolerant to a much wider range of substrates.[15,16]

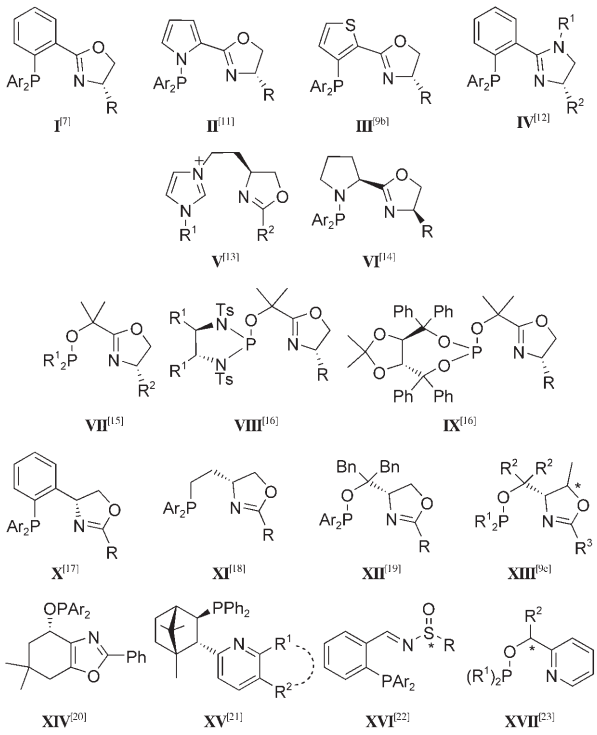
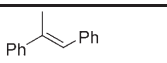
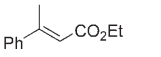
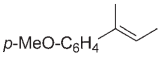
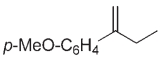
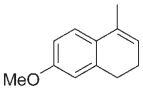
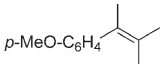
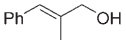
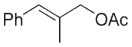


Figure 3. An overview of conceptually important ligands.

Other reports have described variations of the oxazoline moiety, such as moving the anchor point on the oxazoline from the 2- to the 4-position **X**–**XIII** (Figure 3), with great success.[9e,17–19] This small modification has a dramatic effect in that it alters the chiral environment around the Ir atom; thus the fact that different results are obtained should come as no surprise.

More recent publications have conceived new variants on Crabtree's original catalyst, taking advantage of aromatic N-

Table 1. Comparisons of enantioselectivities of substrates with respect to ligands.[a]

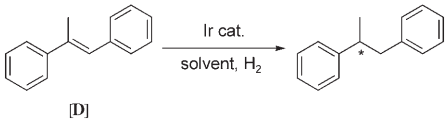
Entry	Substrate	I	II	IV	V	VII	X	XIII	XIV	XV	XVII
1		99	99	94	99	99	99	99	99	95	97
2		84	92	–	–	94	9[b]	94	93	58	99
3		81	75	90	95	98	–	99	99	–	87
4		60	–	54	90	59	–	89	97	–	–
5		72	92	91	–	95	–	85	95	–	–
6		81	–	–	–	–	–	–	37	–	81
7		96	95	–	–	97	–	–	98	69	96
8		91	–	–	–	–	–	–	99	80	–

[a] All *ee* values are taken from the appropriate references. [b] Methyl ester used instead of ethyl ester.

coordination, **XIV**, **XV** and **XVII** (Figure 3).[20,21,23] The Ir complex of **XIVa** (**XIVa**; Ar = *o*Tol) is able to reduce virtually all substrate classes reported thus far, except tetrasubstituted olefins (see below) with excellent selectivities and conversion.[20] In 2004 Ellman reported the interesting ligand **XVI**, a chiral N,P-sulphinyl–imine compound.[22] This while not being the most efficient ligand for the Ir-catalysed hydrogenations of olefins, 94% *ee* in the case of α-methyl-*trans*-stilbene [**D**], is of interest as it incorporates heteroatom chirality. Some of the ligands for example, **I**, **III**, **VI**, **XI** and **XIII**, have been used for the Ir-catalysed hydrogenation of prochiral heteroatom substrates such as imines,[9] with good to excellent activity and selectivity; however, these are beyond the scope of this article. More recently, 2005, Charette and Legault used [**B**] as a catalyst for the reduction of N-iminopyridinium ylides with promising results.[10]

Substrates

Most of the compounds shown in Figure 3 gave an excellent performance with a typical conversion of 100% and *ee* values in the range 90 to ≥99%, when utilised as ligands in the Ir-catalysed hydrogenation of *E*-unfunctionalised trisubstituted olefins, for example, [**D**] (Scheme 1 and entry 1 in



Scheme 1. Hydrogenation of [**D**].

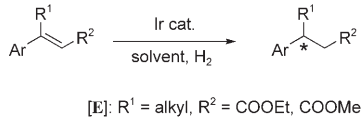
Table 1), under similar conditions (CH_2Cl_2, RT, 50 bar H_2, 0.5 mol%).

Terminal olefins turned out to be rather difficult substrates to be reduced with high selectivities (Table 1, entry 4). Reported selectivities ranged from 60 to 97% *ee* for ligands **Ia** (**Ia**; Ar = *o*Tol, R^1 = *t*Bu) and **XIVa**, respectively.[8,20] An interesting feature of this type of substrate is that temperature and pressure play crucial roles in the selectivity. Burgess reported that at 298 K a decrease in pressure from 85 to 2 bar had a dramatic effect as the selectivity increased from 25 to 90% *ee*, respectively, using ligand **Va** (**Va**; R^1 = 2,6-di-*i*Pr-Ph, R^2 = 1-Ad). However, in sharp contrast, at 85 bar and 258 K an *ee* of 60% was obtained but of the opposite absolute configuration.[13a] Pfaltz has also reported a similar behavior for a number of N,P-ligands showing that pressure and temperature have significant effect on the stereoselectivity.[13b]

While Crabtree's achiral catalyst [**A**][2] is highly efficient in reducing tetrasubstituted olefins, asymmetric versions have only been reported with limited success (Table 1, entry 6).[7,23] The only other catalysts to date that have reacted with both high conversion and selectivity are the cationic zirconocene complexes reported by Buchwald.[24] More interesting substrates are the weakly coordinating functionalised olefins such as the allylic alcohols, α,β-unsaturated acetates, *trans*-β-cinnamic esters, phosphonates and unsaturated enamides since they allow for further functionalisation.

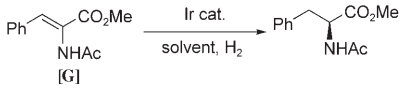
Allylic alcohols have only briefly been investigated and the substrate range is highly limited.[7,8] To date the highest reported *ee* for *trans*-2-methyl-3-phenyl-prop-2-ene-1-ol is 98% by Andersson and co-workers, using ligand **XIVa**, (Table 1, entry 7).[20] However, other ligands gave similar levels of selectivity and conversion.[11,15,19,23] In the case of the acetylated protected alcohol, ligand **XIVa** still performs with the highest selectivity (Table 1, entry 8).

Other examples of weakly coordinating olefins, where the substrate scope has yet to be fully explored, are the allylic esters [**E**][8] and phosphonates [**F**][25] (Scheme 2). In these cases the chiral centre is now the benzylic carbon (Scheme 2) as opposed to the allylic alcohols and acetates. Goulioukina et al. recently reported the successful reduction of a phosphonate analogue of Naproxen, a nonsteroidal anti-inflammatory drug (NSAID), in 95% *ee*.[25]



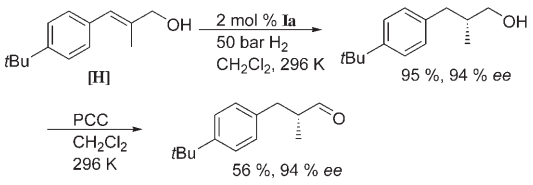
Scheme 2. Hydrogenation of allylic esters [**E**] and phosphonates [**F**].

Knochel et al. have demonstrated that amino acid derivatives can be obtained from enamides such as [**G**] in 96% *ee* using ligand **XVa** (**XVa**; $R^1 = R^2 = H$) (Scheme 3).[21] This is of interest as this allows for the potential Ir-catalysed reaction of highly enantiomerically pure nonnatural α-amino acid derivatives, which have been previously extensively studied with Rh and Ru catalysts.[26]



Scheme 3. Knochel's reduction of unsaturated enamides.

Pfaltz et al. have reported the asymmetric synthesis of the artificial fragrance lilial; when utilizing **Ia** the subsequently formed Ir complex was able to reduce [**H**] in 94% *ee*, which was then subsequently oxidised to the corresponding aldehyde lilial (Scheme 4).[7]



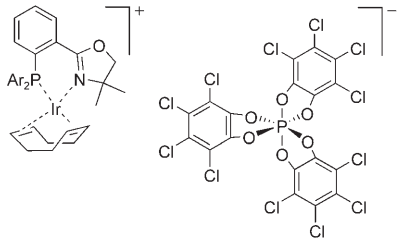
Scheme 4. Enantioselective synthesis of lilial.

Mechanism

Anion effect

Coordinating anions such as halides result in Ir catalysts with lower activity, when compared with weakly coordinating anions, for example, PF_6^-, BF_4^-, and $CF_3SO_3^-$.[27] Pfaltz et al. observed a large decrease in the reaction rate of the following series, $[Al\{OC(CF_3)_3\}_4]^- > BAr_F^- > [B(C_6F_5)_4]^- > PF_6^- \gg BF_4^- > CF_3SO_3^-$.[28] Complexes with the PF_6^- anion suffer from deactivation and water sensitivity, especially at low catalyst loadings (see above).[7] While the *super*-weakly coordinating anions such as $[Al\{OC(CF_3)_3\}_4]^-$ and BAr_F^- are moisture and air stable, they frequently give TOF values of over 5000 h^{-1} and turnover numbers (TONs) in the range of 2000 to 5000, also remaining active after all substrate has been consumed.[28]

Pfaltz et al. observed that the resulting product was racemic, when Δ-TRISPHAT[29] was used as a chiral anion to the achiral Ir-cationic complex **XVIII** (Figure 4) in the hydrogenation of [**D**].[28] However, when the Ir complex formed with **Ib** (**Ib**; Ar = Ph, R = *i*Pr) and the same anion, Δ-TRISPHAT, was used, the product had essentially the same optical purity as for the corresponding BAr_F complex.[7,28] This implies that the anion plays no part in the enantioselective determining step(s) of the catalytic cycle, as otherwise a small effect should be expected.[28]



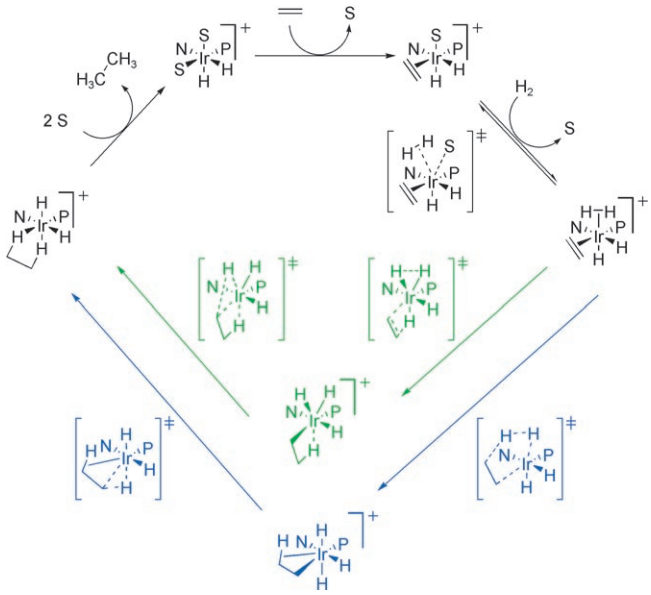
XVIII

Figure 4. Use of the chiral anion Δ-TRISPHAT.

Catalytic cycle

Recently new detailed mechanisms for the Ir-catalysed hydrogenation of olefins have been suggested which differ from the original proposal.[30] Several recent experimental and computational studies have arrived at different conclusions on the catalytic cycle (Scheme 5). The elucidation of the mechanism has been further complicated by the observation that different pathways seem to operate depending on temperature, hydrogen pressure and substrate. For certain systems these effects can sometimes have a significant impact on the stereochemical outcome of the reaction (see above).[13]

Deuterium labeling studies have shown that significant amounts of deuterium are incorporated in the allylic positions of the double bond, which indicates the formation of Ir–allyl intermediates and/or double-bond migration for a number of substrates.[18]



Scheme 5. Catalytic cycles investigated.

Despite all these complications, many highly enantioselective catalysts have been reported and it is likely that most of them can efficiently discriminate between competing reaction pathways.

In a combined experimental and theoretical study by Brandt and co-workers, an Ir^{III}–Ir^{V} catalytic cycle was proposed (Scheme 5, green cycle).[31] The catalytic cycle starts with a solvated iridium–dihydride complex; then the two solvent molecules are replaced by an olefin and molecular hydrogen. The rate-determining step is the migratory insertion of the olefin into an Ir–hydride bond, a step that is energetically favored by the simultaneously oxidative addition of the coordinated hydrogen molecule. Subsequently, the reductive elimination of the saturated hydrocarbon completes the catalytic cycle.

In the similar mechanism proposed by Burgess and Hall,[32] the catalytic cycle also involves an iridium–dihydride species, but the olefin reacts in a metathesis reaction with the coordinated H_2 resulting in a σ-alkyl–Ir^{V} complex (Scheme 5, blue cycle). This compound then undergoes fast reductive elimination to give the reduced olefin. Burgess et al. have further postulated the existence of an Ir^{V} intermediate from a kinetic study of the hydrogenation of 2,3-diphenylbutadiene.[33]

Chen et al. have studied the reaction between an Ir catalyst, using ligand **I**, H_2 and styrene by means of EI tandem mass spectrometry.[34] Under the reaction conditions, found in the mass spectrometer, they were able to find ions from reaction intermediates and proposed that the reaction proceeds via an Ir^{I}–Ir^{III} dihydride cycle. Ions with the composition $[(\mathbf{I})Ir(styrene)(H_2)_2]^+$ were also detected; an intermedi-

ate which could arise from any of the catalytic cycles mentioned.

Selectivity model

Detailed knowledge of a reaction mechanism can often enable a prediction on the sense of the enantioselectivity of a given process. Despite the relatively large number of ligands that have been developed for the asymmetric Ir-catalysed hydrogenation of olefins, only two selectivity models have been proposed so far. Brandt and Andersson proposed a model that correctly predicts the enantiofacial selectivity for a broad range of substrates using the phosphinooxazole ligands **XIV**.[20] The lowest energy conformation of the selectivity-determining transition state was located by means of DFT calculations.[20] In this transition state, the ligand forms a pseudo-C_2 symmetric chiral pocket in which the olefin is coordinated *trans* to the phosphorous and oriented in such a way that the smallest substituent points towards the sterically demanding aryl group on the oxazole (Figure 5). Hence,

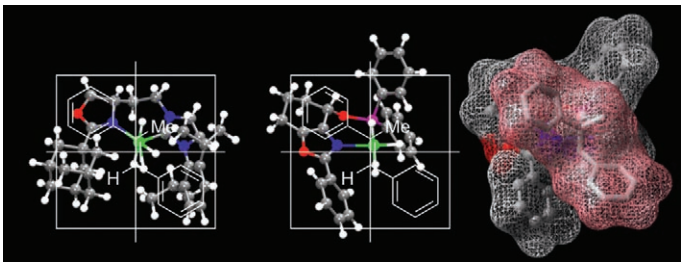


Figure 5. Selectivity models, using optimised transition states and schematic substrate molecules. Left: Burgess et al., centre: Andersson et al., right: structure of the selectivity-determining transition state.

the enantioselectivity of the reaction is controlled by the relative steric interactions of the substrates, thus explaining the opposite absolute configuration and lower selectivity observed in the case of *Z* versus *E* isomers.[8,20]

Burgess and Hall have proposed a similar model for the carbeneoxazoline ligands **V**; in this case the olefin occupies the coordination site *trans* to the carbene moiety.[32] The orientation of the olefin is then governed by the bulky adamantyl in the same fashion as for the oxazole ligands **XIV**.

Outlook

It is our strong believe that interest in the field of iridium-catalysed asymmetric hydrogenation of weakly coordinating olefins will continue to expand, since we have only seen the beginning of catalyst development and the scope of suitable substrates. Since the first report by Pfaltz in 1998, the evolution of the ligand design has always been on the forefront. Only recently have other ligand designs been reported which mimic Crabtree's achiral Ir complex with the same high levels of selectivity and conversion.

However, there still remain many classes of substrates where only limited examples have been reported with satisfactory results. To fully comprehend the limitations and allow future development of this reaction, a better understanding of the mechanistic aspects of the catalytic cycle are required, that is, the questions concerning the different proposed mechanistic steps need to be further investigated and refined.

Hopefully further developments will pave the way for a routine application of these Ir catalysts as versatile catalysts in the chemists toolbox, for example, in natural product synthesis or in industrial scale production of enantiomerically enriched drugs and fine chemicals.

Acknowledgements

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